Gene Therapy

Why Lipid Nanoparticles Are The Future Of Gene Therapy, And What Needs To Happen Next

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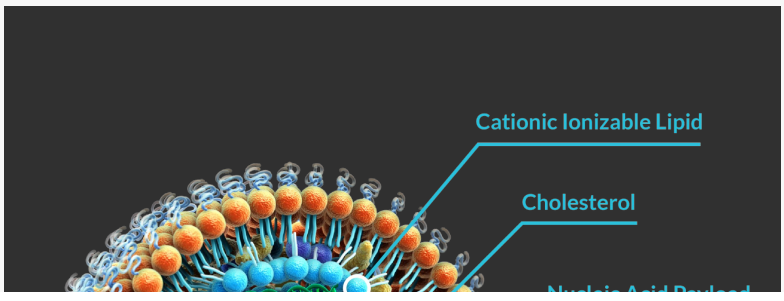
If there has been just one good thing to come from the COVID-19 pandemic, it has been the coming of age of gene therapy. After being seemingly stuck in limbo for decades, gene therapy technology suddenly went from being relegated to treating a handful of rare conditions, to being put into vaccines that would be taken by billions. Gene therapy has the potential to revolutionise medicine because of the precision of its effects. Rather than trying to treat a disease with drugs, which can bind to receptors on the surface of a cell and set off a cascade of effects with undesirable consequences, gene therapy tells the cell exactly what to do using the language of life: the genetic code. By delivering DNA or RNA, gene therapies can allow cells to build proteins that they lack the ability to build, block the production of a harmful protein, or guide 'genetic scissors' to cut diseased genes out of the genome.

Genetic material can't simply be injected into the body on its own – it would have no way of entering our cells, where it needs to be in order to have its intended effect. Instead, the genetic information must be packaged up in some kind of structure that can safely transport it to the target cells. The genetic material then needs to get into the cell and, potentially, into the nucleus itself where the DNA is stored. This is where things can get tricky.

What Are Lipid Nanoparticles?

The gene therapy-based COVID-19 vaccines used one of two delivery systems, or *vectors*, to get genetic material encoding the spike protein into cells. Some, such as AstraZeneca's or Jonson & Jonson's, used a type of virus called an adenovirus to deliver DNA to the cell nucleus. Viruses have evolved to be good at getting into our cells and making them read their viral genetic material, and they can do the same thing for gene therapies. However, adenoviruses have a few problems. While adenoviruses used in gene therapies have been altered so that they cannot multiply to cause disease, they're still viruses, and can still be recognised and attacked by the immune system. This is much more dangerous for the viruses than it is for the human: if the immune system is destroying the adenoviruses before they can deliver their payloads, then the gene therapy won't reach enough cells to be effective. Adenoviruses are also too small for certain applications, with some genes being too large to fit inside the adenovirus vector.

The other delivery method, used by the likes of Pfizer and Moderna, was to use vectors called lipid nanoparticles (LNPs) to deliver messenger RNA coding for the spike protein. If DNA is the 'master copy' of the cell's genetic code, mRNA is the temporary template that is referenced when building a protein. LNPs are tiny 'bubbles' of membrane that can be as small as 60 nanometres across – over 100 times smaller than a red blood cell. The membranes of LNPs are made from lipids similar to the molecules that make up the membranes of all of our cells. These lipids carry an electric charge at one end, making them attracted to water and other charged molecules, but their other ends are long uncharged fatty acids, which are attracted to organic molecules. This allows bubbles of lipids to form a powerful barrier between an aqueous environment (such as the blood) and their contents, regardless of whether that content is made up of charged molecules or not.



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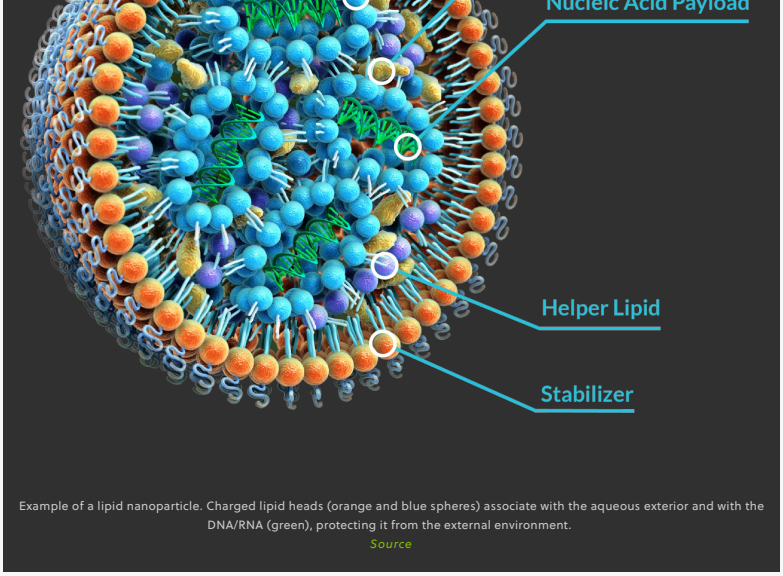


Example of a lipid nanoparticle. Charged lipid heads (orange and blue spheres) associate with the aqueous exterior and with the DNA/RNA (green), protecting it from the external environment.
Source

What Makes LNPs So Promising For Delivering Gene Therapies?

The beauty of lipid nanoparticles is their versatility. The same LNP can be used to deliver DNA or messenger RNA in order to tell cells to make a new protein, or can be used to deliver other types of RNA capable of blocking the production of a protein. This means that LNPs can serve as a 'platform technology' that could allow new gene therapies to be developed very quickly. Once the protein that needs to be produced or blocked is known, the necessary genetic material could be synthesised in a few months and loaded into the appropriate LNP in a few days.

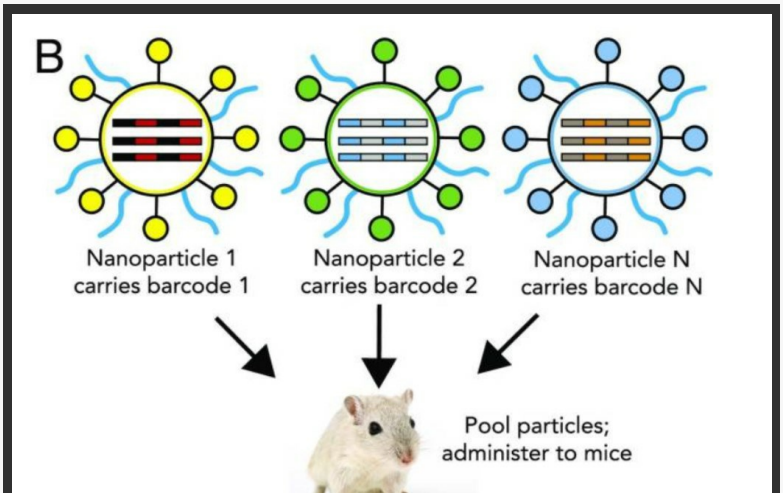
LNPs come in a variety of sizes for accommodating different payloads, and their properties can be changed by altering the composition of the lipid layers in order to change how and, more importantly, *where* the LNPs are absorbed within the body. Current LNPs are mainly absorbed by the liver, but recently, scientists were able to make LNPs target the lungs or spleen instead by adding a fifth charged lipid to the typical four lipid LNP components.

mRNA COVID vaccines have shown that LNPs can be produced reliably on a large scale, which is an important consideration when it comes to the viability of a therapy. LNPs are also less immunogenic than viral vectors (they do not produce as large an immune response).

The Main Problem With LNPs And How To Move Forward

A delivery system can be very good at getting gene therapy into cells, but they have to be the correct cells. A gene therapy designed to cure a kidney disease isn't going to do much if the LNPs carrying it all get absorbed by the liver instead. Unfortunately this is still a major barrier for gene therapy vectors, including LNPs. LNPs tend to be preferentially absorbed by the liver because they look a lot like something else the liver routinely absorbs: lipoproteins, the structures that transport cholesterol and other lipids around the blood.

As mentioned earlier, it is possible to alter where within the body LNPs will end up by changing their composition. However, discovering LNPs that can effectively deliver gene therapy to a target tissue is no easy task. Unlike with conventional drugs, there's almost no relationship between whether an LNP gene therapy works on cells in a petri dish, and whether it works in a living organism. That's because factors that affect LNP effectiveness, such as blood supply and the immune system, aren't present in a petri dish. This means that formulating thousands of LNPs and screening them for effectiveness in cell cultures is off the table. Doing the same thing in animal models would be possible, but would take a very long time and would be very costly.

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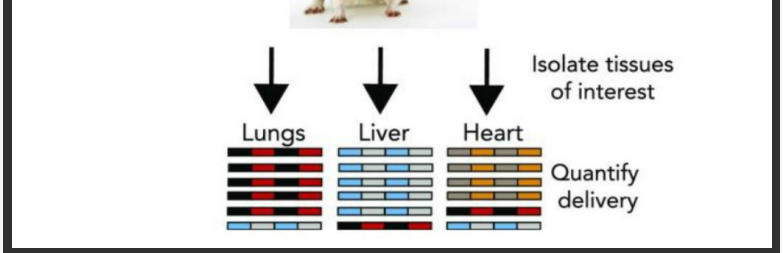

Different LNPs are loaded with unique genetic barcodes and given to the same animal. Researchers can then study which LNPs are successfully reaching which tissues.
Barcoded nanoparticles for high throughput in vivo discovery of targeted therapeutics

Some scientists are working on solutions to this screening problem. One elegant solution shown above is to test multiple LNPs simultaneously in the same animal. In 2017 researchers figured out how to do just that: different LNPs can be loaded with a unique DNA 'barcode' which can then be searched for in the cells of the recipient animal to work out which LNPs are reaching which tissues. Techniques like this should greatly accelerate the discovery of new LNPs with interesting properties. As we learn more about LNPs and how changing the chemical properties of their lipids affects their behaviour, we should be better placed to design new LNPs for specific purposes.

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